TITLE OF THE INVENTION

[0001] Compositions For Improving Mental Performance

CROSS REFERENCE TO RELATED APPLICATIONS

[0002] This is a continuation of International Application No. PCT/US02/21062, with an International filing date of July 3, 2002, which International Application claims the benefit of U.S. Provisional Application No. 60/302,653 filed on July 5, 2001, both of which applications are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0003] This invention pertains, in general, to the field of nutritional-dietary/herbal-botanical, neuro-support factors designed or intended for the sustenance of optimal healthy mental cognition. In particular, the present invention provides formulas for producing compositions for the structural/functional nutritional support for those who struggle with poor focus, concentration and/or memory. In addition, the present invention provides compositions comprising nutritional/botanical factors helpful to those who subjectively experience transient mental fatigue or poor cognitive function.

BACKGROUND OF THE INVENTION

[0004] All journal articles, other references, patents, and patent applications that are identified in this patent application are incorporated by reference in their entirety.

[0005] The role of nutrition and the positive influence of dietary-nutritional, herbal-botanical ingredients as they relate to optimal energy production, neurophysiology, and neurotransmitter synthesis/formation cannot be understated.

[0006] Physiology textbooks describe the brain as the most metabolically demanding of all organs (86). Representing only 2% of the total body weight, the brain consumes 50% of the circulating blood glucose, and over 20% of circulating oxygen. In essence, neurons have energy needs more than twice that of other cells. Since neural requirements for energy substantially exceed that of other cells in the body, Krebs-Cycle intermediates are metabolically essential ingredients for optimal ATP generation, optimal neural metabolism, and thus, improved mental acuity.

[0007] Also, neurotransmitters are naturally occurring molecules that act as biochemical messengers relaying nerve signals between neurons. Adequate production of the different types of neurotransmitters is responsible for proper mental functioning. Deficiencies of these neurotransmitters interfere with behavior, mood, concentration and memory.

[0008] Based on the brain's need for energy production and neurotransmitter synthesis, scientists postulate that the chemistry of our diet is a critical element in the subsequent triggering of neurotransmitter synthesis and efficient energy production, which jointly lead to normal/optimal cognitive function. Thus, a new class of research has evolved that investigates the effect of various dietary, nutritional and herbal constituents known to improve learning and memory. This class of "smart nutrients and foods" has been termed *nootropics* – meaning literally "toward the mind."

[0009] Exhaustive analytical investigation into nootropics has been ongoing, and several studies have confirmed the necessity of several key nutritional ingredients to mental health. In particular, researchers at the United States Department of Agriculture (USDA) mounted a study to examine how marginal nutritional deficiencies affect memory and mental function. They meticulously determined the nutritional status of twenty-eight healthy people age sixty and older, and then gave them challenging mental tasks to measure cognitive function. Significant relationships were noted between nutritional status and test performance. Subjects who had optimal levels of certain nutrients tested better than those with nutrient deficiencies. The nutrient groups' electrocardiogram (EEG) rating, which assesses activity in the brain, indicated superior brain functioning. This study suggested that even mild nutritional deficits might be responsible for cognitive decline and changes in brain function. The strongest associations were with thiamine (vitamin B1), riboflavin (vitamin B2), and iron. Beta-carotene, vitamin C, and zinc levels were also predictive of performance on mental function tests (1).

[0010] A much larger, long term study performed at the University of New Mexico School of Medicine followed 137 people between age sixty-six and ninety for six years. The participants in this study were educated, well nourished and had no memory problems. Their vitamin status was determined at the beginning of the study and again after six years. At the study's conclusion they were given tests determining

cognitive function. Test performance was related to past and current nutritional status, and significant associations between mental function and vitamin status were noted. Those in the study group who had higher blood levels and intake of vitamins in the B-complex family (thiamin, riboflavin, niacin, and folate) performed better in tests of abstract thinking. High blood levels of vitamin C were associated with increased ability in performing visual and spatial tasks, and higher intakes of vitamin E, A, B6 and B12 correlated with better scores on both visual and spatial tasks, and higher intake of vitamins E, A, B6, and B12 correlated with better scores on visual and spatial recall and/or abstract thinking. The participants in this study who, on their own, had taken vitamin supplements, did better on difficult visual and spatial tests and on tests of abstract thinking (2).

[0011] In many children and teens, daily nutritional supplementation has shown to manifest profound cognitive benefits. For example, adding nutritional supplements to the diet has resulted in increased intelligence in children, even in the absence of malnutrition or poor cognitive function (24). In some cases, the benefits include the resolution of many of the symptoms associated with various learning disabilities, including attention deficit disorder (ADD), which is a term currently used to describe a condition that has had multiple labels in the past. Currently, more than ten prominent studies have shown that learning disabled/ADD children and adults suffering with similar symptomatology have special dietary needs for DHA (docosahexaenoic acid), thiamine, vitamin C, pyridoxine, calcium, magnesium, iron and zinc (27, 28, 29, 30, 31, 32, 33, 34, 35). In many of the previously referenced studies, when these nutrients are added to the diets of subjects suffering with learning disabilities/ADD, some symptoms are shown to significantly diminish, and in many cases resolve.

[0012] This invention provides unique formulas of nootropic nutrients and herbal extracts designed to provide specific dietary-nutritional and herbal-botanical support factors for cognitive function. Administration of the compositions based on these formula results in the efficient formation of mental energy and the synthesis of key neurotransmitters associated with memory, focus and concentration. The present formulas have increased bioavailability of constituent components and therefore have an enhanced synergistic affect on mental health.

[0013] The ingredients of the present invention are necessary constituents, co-factors and synergists in the formation and synthesis of the following energy substrates and neurotransmitters: acetylcholine, serotonin, dopamine, norepinephrine/epinephrine and adenosine triphosphate (ATP). All of these neurotransmitters and energy factors are intricately involved in mental cogmtion, neurological (as well as systemic) metabolism, the regulation of mood, and the ability to focus and concentrate, as well as learning, memory and numerous creative and analytical cognitive processes.

[0014] As a convenient addition to the daily diet, the formulas of the present invention provide a unique combination of energy precursors, neurological support antioxidants and nutrients, as well as many nootropic ingredients in their most bio available/absorbable forms to provide enhanced efficacy.

SUMMARY OF THE INVENTION

[0015] The present invention provides compositions formulated to provide support for mental performance and/or improve mental performance through the elimination of mental fatigue, as well as to improve memory, focus and concentration.

[0016] The present invention provides novel, comprehensive multi-vitamin/mineral formulas providing unique combinations of nutrient sources derived from "Krebs Cycle Intermediates." These sources of ingredients are more absorbable than ordinary sources of nutrients and thus, more likely to show an improvement in blood nutriture. In addition, these sources of nutrients provide precursors for ATP formation.

[0017] An unprecedented and quite notable feature is the fact that the present invention provides a unique combination of specific cognitive support factors. Although individually many of the nutrients have been clinically shown to enhance mental energy levels as well as support and enhance mental focus, concentration and memory, these nutrients have an enhanced synergistic affect when combined within the present composition.

[0018] The present invention constitutes novel, proprietary formulas designed to provide specific dietary-nutritional, and herbal-botanical support factors for cognitive function through the efficient formation of both mental energy, and the synthesis of key neurotransmitters associated with memory, focus, concentration and mood. The

present also provides compositions and methods for the administration of the formulas of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

I. General Description

[0019] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

[0020] The current inventions in this application are in the fields of nutritional supplements and methods of using such supplements to improve and maintain memory, focus, concentration and mood.

[0021] The Detailed Description and Examples provide detailed scientific results that can be used by a skilled artisan to prepare and administer the compositions of the present invention. The description of the present invention provided herein has been given for clearness and understanding only and no unnecessary limitations should be understood therefrom as modifications will be obvious to those skilled in the art.

II. Components Of The Composition

[0022] The composition of this invention consists primarily of the following ingredients: B-complex vitamins, antioxidants, minerals, phosphatidyl serine (PS), choline, dimethyl-aminoethanol (DMAE), docosahexaenoic acid (DHA), L-pyroglutamic acid, as well as herbal extracts from *Bacopa monniera, Vinca minor* and *Huperzia serrata.* Each of these components is more clearly defined below.

A. B-Complex Vitamins

[0023] Among the most important nutrients known to be involved in maintaining optimal mental function are the B-complex vitamins. These nutrients play both direct and indirect roles in neurological function. The indirect role the B vitamins play in cognitive function are underscored by their involvement on methylation – the process by which toxic byproducts of cellular metabolism are removed from the body.

[0024] Methylation is the body's chief mechanism for detoxification. It is in essence, housecleaning on the cellular level. When this process goes awry, there is a buildup of highly toxic homocysteine (a byproduct of normal amino acid metabolism). Elevated homocysteine is shown to result in viscous blood (resulting in decreased neural and systemic oxygenation), increased free radical pathology, initiates and accelerates arteriosclerosis, cancer, neuro-vascular decline, neuro-degenerative disorders, and is a marker for memory loss, cognitive dysfunction and Alzheimer disease (3, 4, 5). The process of optimal methylation can be nutritionally supported, and toxic levels of homocysteine can be reduced and eliminated by the consumption of specific B-complex vitamins (3, 4, 5, 6). In addition, studies show that people with the highest blood nutriture of B-complex vitamins score highest on tests of cognitive function (3).

[0025] In addition, B-vitamins are known as nutritional cofactors that act as biochemical "spark plugs" in mitochondria, and therefore act to further nurture and support optimal neural metabolism. The present invention incorporates unique metabolically enhanced forms of B-vitamins. The B-vitamin complex is present in the inventive formulation at about 1% to about 10% of the overall composition. Constituents of the B-complex contemplated by the present invention are further described below.

[0026] Folic acid is a collective term for pteroylglutamic acids and their oligoglutamic acid conjugates. Supplemental folic acid is important for men, women and children of all ages. Mild deficiencies have been found to be associated with irritability, depression, poor cognitive function and memory loss (3, 4, 7, 8, 9). Deficiencies are quite common in the population (7, 8, 9). Folic acid may comprise about 400 micrograms ("mcg") of the overall composition. Preferably from about 100mcg to about 1000mcg, more preferably from about 200mcg to about 800mcg, and even more preferably from about 400mcg to about 600mcg. Vitamin B1 (thiamin) was the first of the B vitamins to be discovered. It is required for the production of multiple enzymes that are necessary for the conversion of glucose into energy in the brain. This nutrient also mimics the activities of acetylcholine – the major learning neurotransmitter associated with attention, concentration and memory. Increased thiamin consumption is associated with improved cognitive function and faster

reaction times, with participants subjectively describing supplementation effects as "feeling clearheaded, composed, and energetic" (1, 2 , 4, 7, 10). Vitamin B1 may be present in the overall composition as thiamin, preferably from about 1mg to about 25mg, more preferably from about 2mg to about 20mg, and even more preferably from about 3mg to about 10mg.

[0027] It is also important to note that vitamin B5 (pantothenic acid) must be present for the synthesis of acetylcholine. The present herbal composition may contain Vitamin B5 as calcium pantothenate and/or pantethine, preferably as d-calcium pantothenate. Vitamin B5 may comprise preferably from about 10mg to about 100mg, more preferably from about 12mg to about 25mg and most preferably from about 12 to 16mg.

[0028] Niacin (vitamin B3) is necessary for the production of energy. In neurological tissue, niacin is located both in nerve cell membranes, where it helps facilitate nerve impulse transmission, and inside neurons (brain cells), where it is involved in metabolism and oxygen supply. A number of studies indicate that supplementing this nutrient improves brain function. For example, participants were tested in a double blind study for effects on short- and long-term memory. Memory tests were performed, and repeated after six weeks and revealed 10 percent to 40-percent improvements in both short- and long-term memory, compared to the placebo group (11). Vitamin B3 may be present in the compositions of the present invention either as inositol hexanicotinate, niacinamide, nicotinic acid and/or nicotinate; preferably inositol hexanicotinate and niacinamide are present in the composition; and most preferably both are present in equal amounts in the composition. Preferably from about 10mg to about 100mg, more preferably from about 15mg to about 50mg, and even more preferably from about 20mg to about 30mg of vitamin B3 is used within the present composition.

[0029] Vitamin B6 (pyridoxine) is required in the production of the neurotransmitters – norepinephrine, serotonin and dopamine. It has been shown to enhance memory and cognitive function, and low levels of this nutrient correspond to poor scores on tests of cognitive function and premature neural aging (2, 3, 4, 12, 13). In addition, deficiencies are not uncommon in the population (2, 3, 4, 12, 13). The Vitamin B6 in the present compositions may be either a pyridoxine, pyridoxal or

pyridoxamine; and preferably Vitamin B6 is present in the composition as pyridoxal-5 phosphate, pyrodoxine and/or 30 pyrodoxine alpha keto-glutarate. Preferably pyridoxal-5 phosphate and pyrodoxine alpha keto-glutarate are present in the composition, and most preferably, pyridoxal-5 phospate comprises 33% of the Vitamin B6 present in the composition and pyrodoxine alpha keto-glutarate comprises preferably from about 33% to about 90%, more preferably from about 40% to about 80%, and even more preferably from about 50% to about 70% of the vitamin B6 present in the composition. In general, Vitamin B-6 comprises preferably from about 5mg to about 100mg, more preferably from about 10mg to about 50mg, and even more preferably from about 12mg to about 30mg.

[0030] Cobalamin, or vitamin B-12, is essentially the neuro-nutrient. It is the most important of the B-vitamins for proper cognitive function. It plays multiple roles, in methylation, production of healthy blood, as well as production of healthy myelin in neurons. Deficiencies are common, and marginal deficiencies are shown to result in depression as well as cognitive decline in the elderly. Scientists conclude that as much as fifty percent of mental confusion, deterioration and cognitive decline in the elderly may be attributed to a lack of this nutrient (1, 2, 3, 4, 5, 6, 14, 15, 16, 17). Although Vitamin B12 is cyanocobalamin by chemical definition, any substituted cobalamin such as adenosylcobalamin, cobalamin, hydroxocobalamin, or methylcobalamin may be used. Preferably, the Vitamin B12 used within the present invention is present as an ion exchange residue of cyanocobalaniinin or a substituted cobalamin. The ion exchange resin is preferred as a result of this form appearing to exhibit enhanced stability. Preferably from about 10mcg to about 100mcg, more preferably from about 12mcg to about 50mcg, and even more preferably from about 15mcg to about 30mg of Vitamin B12 are present in the composition.

B. Antioxidants

[0031] Supplemental antioxidants are critical for optimal mental performance and are present in nutritional constituent and herbal composition preferably from about 10% to about 40%, more preferably from about 12% to about 30%, and even more preferably from about 15% to about 33%.

[0032] For example, in an Austrian study of 1,769 people from ages fifty to seventy five, researchers found that individuals with low blood levels of vitamin E performed more poorly on tests of cognitive function than those with high blood levels of the vitamin (18). The present compositions contain Vitamin E as -tocopherol as well as other isomers of tocopherol and/or tocotrienol. Preferably Vitamin E is present as a d- or dl- isomer of -tocopherol, -tocopheryl acid succinate, or -tocopheryl acetate; most preferably it is present in the composition as d- -tocopheryl. Vitamin E is present in the composition preferably from about 15IU to about 400IU, more preferably from about 20IU to about 200IU, and even more preferably from about 30IU to about 100IU.

[0033] Like Vitamin E, Vitamin A is a fat-soluble antioxidant that plays numerous protectant and physiological roles in the brain. Beta-carotene, a carotenoid, is a precursor to Vitamin A formation, and is converted into Vitamin A as needed. New research suggests that this nutrient is involved in brain function throughout life. Vitamin A has been described by Dr. Ronald Evans of the Salk Institute for Biological Studies in La 10 Jolla, Calif., as "a type of molecular key that unlocks one of the most powerful functions of the human brain, learning" (19). Vitamin A, typically associated with retinol, carotene, especially beta carotene, and carotenoids, is also within the present invention. Preferably the present invention includes beta carotene and other naturally occurring carotenoids. Preferably from about 2000IU to about 5000IU, more preferably from about 2500IU to about 4500IU, and even more preferably from about 4000IU to about 5000IU of Vitamin A are present in the herbal compositions of the present invention.

[0034] Vitamin C plays multiple important roles in cognitive function. As a matter of fact, it is so important to neural tissue that concentrations of Vitamin C are fifteen times higher in the brain than elsewhere in the body. It is also involved in the production of several neurotransmitters, including acetylcholine, dopamine and norepinephrine. Administration of this nutrient has been shown to increase IQ points, and the use of vitamin C to treat memory disorders is currently being explored (1, 2, 4, 7, 18, 20). Vitamin C, ascorbic acid, is also present in the herbal composition. Preferably, Vitamin C is present as ascorbic acid, sodium ascorbate, ascorbyl palmitate, calcium ascorbate, potassium ascorbate and/or zinc ascorbate. Most

preferably each of these is present in the composition in equal amounts. Vitamin C comprises preferably from about 200mg to about 1000mg, more preferably from about 225mg to about 500mg, and even more preferably from about 250mg to about 400mg.

[0035] Also, naturally occurring antioxidants such as oligomeric proanthocyanidins may also be present in the herbal compositions of the present invention. These proanthocyanidins are obtained from fruits, vegeatables, nuts, seeds, flowers, and barks of plants and have been reported to have a broad spectrum of biological, pharmacological and therapeutic activities against free radicals and oxidative stress (87). Proanthocyanidins derived from the seeds and leaves of grapes such as the *Vitis vinifera* variety are incorporated into the present composition. The increased bioavailability of these naturally occurring antioxidants increases the effectiveness of the present composition and therefore makes their incorporation into the composition preferable to that of other proanthocyanidins. Commercially available grape seed extracts such as Activin® produced by InterHealth Nutritionals, Inc. can be used in the present composition. The proanthocyanidins derived from the grape seed and leaves comprise preferably from about 5mg to about 100mg, more preferably from about 8mg to about 50mg, and even more preferably from about 12mg to about 25mg.

C. Minerals

[0036] Minerals are another category of underrated neuro-nutrients that play vital roles in mental function. Normal brain function is dependent on several key minerals that make up only 0.5 percent of the brain by weight. Whereas fatty acids like DHA provide much of the structural bulk of the brain (approximately 70%), minerals constitute a small fraction of its mass. The present composition is comprised preferably from about 10% to about 50%, more preferably from about 15% to about 30%, and even more preferably from about 20% to about 25%.

[0037] Zinc for example, is essential for neural function and also doubles as an antioxidant. Magnesium is a necessary cofactor in over three hundred enzymatic reactions, many of which are essential in the processes of generating neurotransmitters, energy and ATP. The literature shows that iron deficiency, which exists in a significant number of children with learning disabilities, may be a causative factor for much of the symptomatology associated with such poor cognitive function (25, 26).

Several studies have suggested that supplementation with zinc, magnesium and iron among other minerals may provide cognitive protective effects, as well as improve memory, communication, and understanding (1, 21, 22, 23).

[0038] Calcium is a second messenger in neuronal membranes, which means it acts like a traffic signal for uptake and release of neurotransmitters. A "green light" from calcium permits the release of a neurotransmitter into the synaptic intersection. A "red light" halts its passage into the receiving neuron. Calcium also interacts with potassium and sodium to maintain proper levels of nerve-cell stimulation. This is how the balance between nerve cell activation and inactivation is achieved in the brain. In addition, calcium interacts with zinc in the regulation of the neurotransmitter histamine, and is dependent on DHA for all of its membrane functions. Thus calcium, in an elaborate concert with other neuro-nutrients regulates the speed, intensity, and clarity of every message that passes between brain cells.

[0039] Again, these underrated neuro-nutrients are crucial for healthy neurological function that ensures the activation of neuronal communication, regulation of neural metabolism, and protection of the brain against free-radical oxidation and toxic-metal contamination. Of all the minerals, calcium, magnesium, zinc and iron play the largest roles in brain function and constitute most of the mineral content in the brain.

[0040] In order to maximize neurotransmission and thus cognitive function, current research clearly supports the necessity of improving dietary intake of these nutrients. Quite paradoxically however, calcium, magnesium and zinc aggressively compete for uptake in the gastrointestinal tract, increasing the difficulty of introducing a clinically sufficient amount of each into the circulation (and brain) during one nutritionally supplemented meal. Thus, the quantity, and quality of the source of each nutrient becomes a key factor in developing an effective formula to improve nutriture and thus, mental cognition.

[0041] To overcome this common impediment to absorption, and thereby improve the effectiveness of the formulations of the present invention via bypassing the limiting factor of competitive inhibition, all minerals, including the critically important factors for cognitive function are provided in both optimal quantities and from multiple, highly absorbable, non-competitive sources called Krebs Cycle intermediates. These sources provide substantially greater absorption and neurological

activity compared to other more commonly utilized mineral sources (36). Thus, the present composition provides preferably from about 25mg to about 200mg, more preferably from about 30mg to about 100mg, and even more preferably from about 40mg to about 75mg of calcium as calcium carbonate, chelated bisglycinate, calcium gluconate, calcium lactate, calcium phosphate, calcium citrate, calcium ascorbate, and/or calcium succinate. Likewise, preferably from about 50mg to about 400mg, more preferably from about 75mg to about 300mg, and even more preferably from about 100mg to about 200mg of magnesium is contained within the present inventive composition as magnesium oxide, magnesium gluconate, magnesium glycinate, chelated magnesium, magnesium citrate, magnesium malate, and/or magnesium taurinate. Preferably the composition contains magnesium citrate, magnesium malate, and magnesium taurinate. The composition also incorporates preferably from about 25mg to about 99mg, more preferably from about 35mg to about 75mg, and even more preferably from about 40mg to about 60mg of potassium as potassium citrate, potassium aspartate, and/or potassium ascorbate. Zinc may also be present in the composition bound to picolinate, citrate, acetate, gluconate, glycine, monomethionine, chelates and/or ascorbate form. Preferably the zinc is present bound to citrate and ascorbate and comprises preferably from about 5mg to about 30mg, more preferably from about 7mg to about 25mg, and even more preferably from about 10mg to about 20mg. Iron may comprise preferably from about lmg to about 18mg, more preferably from about 2mg to about 10mg, and even more preferably from about 4mg to about 8mg. Typical iron compounds that my be present in the composition are ferrous fumorate, ferrous gluconate, ferrous sulfate, iron dextran, iron bisglycinate, and iron polysaccharide. Ferronyl® from Albion Labs provides a suitable commercial source for iron.

[0042] In addition, to further eliminate the possibility of competitive inhibition, multiple sources of each mineral component are present, preferably the composition includes about seven unique nutrient sources to deliver calcium and magnesium alone. Krebs Cycle intermediates are better absorbed, utilized and tolerated than the common inorganic or relatively insoluble mineral salts, including magnesium chloride, oxide, sulfate and carbonate (36, 37, 38, 39). As previously asserted, the Krebs Cycle intermediates have been carefully selected for the formulas of the present invention so

as to play multiple roles in the generation of energy, and demonstrate a specific affinity for, and activity in the brain. The precise selection, multiple sources and ratios of these ingredients are intended to substantially increase the clinical effectiveness of the formulas of the present invention.

[0043] Additionally, minerals that are not directly linked to the nutritional well being of the brain also assist in its maintenance. For example, iodine is well known for its role in regulating the hormonal output of the thyroid. Since the hormones of the thyroid regulate metabolism and growth, an iodine deficiency has been demonstrated to adversely affect the mental capabilities of an individual in extreme cases leading to cretinism. The consumption of iodine has been directly linked to enhanced mental capabilities (88). The present invention incorporates preferably from about 5mcg to about 100mcg, more preferably from about 7mcg to about 25mcg, and even more preferably from about 10mcg to about 20mcg.

[0044] Preferably the iodine is derived from a natural source such as seafood, seaweed, or plants grown in iodine rich soil. Most preferably, the iodine is derived solely from kelp since it exhibits increased bioavailability.

[0045] Other minerals such as boron, chloride, copper, chromium, lithium, manganese, selenium, and vanadium may also be used within the present composition.

D. Phosphatidyl Serine (PS)

[0046] A supplement that enhances the cerebral cortex output of acetylcholine, phosphatidyl serine (PS) is the neurotransmitter associated with our ability to think, reason and concentrate. In addition, PS stimulates the synthesis and release of dopamine, related to heightened states of attention.

[0047] PS is the major phospholipid in the brain that plays a major role in determining the integrity and fluidity of cell membranes. PS supplementation in both animal studies and human clinical trials has been shown to significantly improve memory, mood and behavior, and to significantly eliminate depression. The most impressive PS studies have shown a marked improvement in cognitive function in the elderly. For example, supplementation with PS indicates that it may reverse up to twelve years of age-related mental decline (40). Furthermore, research demonstrates that PS supplementation results in a 15 percent improvement in learning ability and

memory tasks (41). Human trials dating back to the 1970's support these findings. PS works by activating almost all regions of the brain, as seen in position emission tomography (PET) scans and EEGs (42, 43).

[0048] The present composition contains PS, preferably in the form of a lecithin phosphatidyl serine complex. While there is a bovine source of PS available, at this time the soy based raw material is the preferred raw material supplying PS. An example of a suitable commercially available source of PS would be Leci-PS® 30 P sold by Lucas Meyers. PS comprises preferably from about 2% to about 20%, more preferably from about 4% to about 10%, and even more preferably from about 5% to about 10%. Preferably from about 20mg to about 200mg, more preferably from about 30mg to about 150mg, and even more preferably from about 40mg to about 100mg of PS is used within the composition.

E. Choline/Phosphatidyl Choline

[0049] Classified by the National Academy of Sciences as an essential nutrient in 1998, choline falls into the general category of B-complex vitamins. It is a constituent of cell membranes and an essential precursor to the neurotransmitter acetylcholine – again, one of the brain's most important neurotransmitters associated with heightened states of attention, improved memory and learning.

[0050] Choline has demonstrated effects in humans including improvement in memory, thinking ability and serial-type learning in clinical studies (44). Dr. Christian Gillin, government scientist and top official at the National Institutes of Health, reports "[O]ur tests show that giving people choline increases their memory and learning ability by a startling 25 percent."

[0051] When combined with the B-complex and phosphatidyl serine, the raw materials are present for the formation of phosphatidyl choline – a facilitator of intercellular communication and an important component of nerve cell membranes.

[0052] The present composition contains preferably from about 10mg to about 100mg, more preferably from about 15mg to about 75mg, and even more preferably from about 20mg to about 50mg of choline, or about 1-3% of the overall composition. The choline is present in the composition as a bitartate, citrate, or chloride salt and

phosphatidylcholine. Preferably choline is present in the composition as a choline bitartate.

F. Dimethyl-aminoethanol (DMAE)

[0053] DMAE is a natural substance present in foods such as anchovies and sardines (a reason fish is called brain food). It enhances memory and cognitive function by stimulating the production of choline, which, in turn, improves the synthesis of acetylcholine.

[0054] DMAE was commonly used prior to the 1980s and was especially effective in children with learning or behavioral problems associated with learning disabilities, shortened attention spans and/or hyperactivity (what we now define as ADD) (45, 46, 47, 48). Additional studies demonstrate improved mental concentration and sounder sleep in healthy subjects that consume DMAE (49) .

[0055] In one study, 108 children with a learning disabilities behavior profile were given supplemental DMAE. Improvement was observed in the vast majority (71%) of the learning disabled/hyperactive children in the areas of increased attention span, decreased irritability, scholastic improvement, and, in some children, a rise in IQ (50).

[0056] In addition, DMAE is useful for adults with cognitive complaints. A 1996 German study examined the effects of DMAE along with vitamins and minerals on sixty men and women between the ages of forty and sixty-five who had difficulty concentrating during mental exercises. In this study, researchers obtained EEG recordings of volunteers before they began taking DMAE or placebo, and again after twelve weeks of supplementation. There were no changes in the brain waves in the subjects taking the placebo. In those taking DMAE, however, improvements were seen in the frontal and temporal lobes, areas of the brain that play an important role in attention, memory, concentration, and flexibility in thinking (51).

[0057] This ingredient was sold in the 1950's, 1960's and 1970's. It was marketed by a pharmaceutical company for its proven ability to accelerate mental processes, improve concentration span, and abolish early morning fogginess. It was considered to be more advantageous than amphetamines or stimulants in that it has no effect on heart rate or blood pressure, and DMAE does not induce jitteriness or anorexia (52, 53, 54, 55).

[0058] The present composition contains DMAE, preferably as a bitartrate. It may be present in the complex preferably from about 50mg to about 600mg, more preferably from about 100mg to about 400mg, and even more preferably from about 200mg to about 300mg., or about 5-25% of the overall complex.

G. Docosahexaenoic Acid (DHA)

[0059] The most abundant omega-3 fatty acid present in the brain is DHA. Research has shown DHA to play a critically important role in the integration and regulation of both the structure and neurological function of the brain.

[0060] Structurally, DHA is a long-chain polyunsaturated fatty acid with six double bonds, making it a hot bed of chemical and electrical activity. DHA is concentrated in the synaptic gaps between axons and dendrites, where neural communication takes place. It is also abundant in the neurons' mitochondria where ATP production takes place. In essence, where reasoning, learning and memory abound, there is an abundance of DHA.

[0061] Low levels of DHA are associated with a myriad of mental dysfunction including depression, aggression, memory loss, early dementia and Alzheimer's disease (56, 57). Interestingly, in many cases, depression, aggression and memory loss are shown to significantly improve, if not completely resolve, with the addition of this fatty acid to the diet. In addition, current research indicates that chronically low consumption of this fatty acid has been shown to be directly involved in some ADD/ADHD symptoms (28, 31, 32). For example, one study showed that a deficiency of DHA actually produced ADD/ADHD symptoms and demonstrated that children suffering with these symptoms had a marked reduction of DHA levels in the blood (28). Simply improving the blood level of this nutrient is shown to improve memory, visual acuity, and help maintain a positive mental state (28).

[0062] DHA is present in the composition. Preferably DHA concentrate fish oils 15% make up preferably from about 20mg to about 200mg, more preferably from about 30mg to about l00mg, and even more preferably from about 40mg to about 60mg of the composition, about 4% of the overall composition.

H. L-Pyroglutamic Acid

[0063] The amino acid L-Pyroglutamic acid helps maintain the sensitivity of receptor sites to acetylcholine at the post-synaptic gap between neurons. A given amount of acetylcholine will then have a larger, more pronounced effect, thereby enhancing neuroreceptor performance. Supplements of L-Pyroglutamic acid have been shown to enhance the ability to remember, focus and learn (58, 59).

[0064] In addition, L-Pyroglutamic acid is used as a building block for three related neurotransmitters: glutamic acid, l-glutamine and gamma-amino buteric acid (GABA). GABA is an amino acid that is essential for brain metabolism, aiding in proper brain function. Together with niacinamide and inositol, it prevents anxiety and stress related messages from over-stimulating the motor centers of the brain, thus providing a focused, centered and calming effect.

[0065] The present invention contains preferably from about 25mg to about 500mg, more preferably from about 40mg to about 250mg, and even more preferably from about 50mg to about 100mg of L-Pyroglutamic acid, about 2-3% of the overall composition, and preferably contains about 10 mg of GABA, about 1% of the overall composition, as well.

I. *Bacopa monniera* (Bacosides)

[0066] *Bacopa monniera* is a traditional Ayurvedic herb utilized in India for more than 3,000 years to enhance memory capacity, improve intellectual and cognitive functions, reduce stress-induced anxiety and increase concentration.

[0067] *Bacopa monniera* has been shown to be a useful agent in reversing the symptoms of mental dysfunction in children (60) as well as a long history of research and use. The active ingredient in *Bacopa monniera* (called bacosides) is shown to regulate and restore proper synaptic activity in over-stimulated neurons, among other benefits.

[0068] Two active molecules with memory-enhancing properties were isolated from this plant and their chemical structures were determined; bacosides A and B (61).

[0069] Bacopa extracts have been shown to facilitate the acquisition, consolidation, retention and recall of learned tasks (62, 63). Research at Central Drug Research Institute (CDRI) showed that regular consumption of bacosides A and B extracted

from the bacopa plant increases the protein kinase activity and new protein synthesis of the brain cells involved with learning and memory (64). The bacosides have also been shown to help repair damaged neurons by augmenting kinase, the protein involved in the synthesis of new neurons to replace old ones (64). As a result, depleted synaptic activity is restored leading to enhanced brain and memory function (65, 66).

[0070] Studies have shown that a student's concentration while studying is at its optimum during the first hour. However, in the second hour, concentration is reduced to 50 percent and by the third hour concentration is further reduced to 25 percent. Studies conducted by CDRI have conclusively shown that the concentration of students taking bacopa is maintained at optimum levels for three hours or more (62). Bacopa also increases mental retention. In normal circumstances, retention is 55 percent (*i.e.*, 1 in 2 learned tasks are forgotten). However, after taking a standardized bacopa extract for a period of three months, the retention levels were shown to increase to 95 percent (*i.e.*, only 1 in 20 learned tasks are forgotten)(62).

[0071] In 1993, Dr. Dubey and his team studied the effect of bacopa extracts in a placebo-controlled trial involving 232 children with mild to moderate mental deficiency. Significant improvement in both short-term and long-term memory was seen after daily therapy for one year, and significant improvement in memory was seen as early as three months following supplementation (67).

[0072] Bacopa extracts, preferably derived from the leaves of *Baccopa monniera*, are used within the present composition. Additionally, commercially available bacopa extracts such as Bacopin® manufactured by Sabinsa Corporation may be used. Bacopa extracts are present in the composition preferably from about 25mg to about 200mg, more preferably from about 40mg to about l00mg, and even more preferably from about 40mg to about 80mg.

J. *Vinca minor* (Vinpocetine)

[0073] Another effective plant-derived nootropic is vinpocetine. This herbal extract comes from the lesser periwinkle (*Vinca minor*). Vinpocetine has been shown to improve blood flow, circulation and oxygen utilization in the brain of animals and humans (68, 69, 70). It also protects neurons from the devastating effects of disrupted

oxygen delivery. It is, therefore, a useful therapy for symptoms of senile dementia and cerebral vascular insufficiency (71, 72, 73, 74, 75).

[0074] Researchers at the University of Surrey in England administered either a high or low dose of vinpocetine or placebo to 203 patients with mild to moderate dementia. Significantly greater improvements were observed in cognitive performance and overall quality of life in the patients taking vinpocetine compared to the placebo group. Interestingly, there was little difference in the degree of improvement between those taking the high and low doses of the herb (76).

[0075] Vinpocetine also improves energy production in brain cells. It has been studied as a memory booster for young, healthy people, in whom it has been shown to improve short-term memory. In addition, it appears to have anticonvulsant properties. A Russian study of epileptic patients demonstrated that vinpocetine reduced the frequency and, in some cases, completely eliminated epileptic seizures in twenty of the thirty-one patients involved in the study. This nontoxic herbal extract was well tolerated in the bulk of participants in all of the clinical studies.

[0076] While many studies focus on the effects of vinpocetine for patients suffering from various degenerative conditions, researchers have also demonstrated positive effects in healthy individuals. In the United Kingdom, clinical trials in hundreds of individuals have shown that vinpocetine improves memory, including marked improvements in young and middle aged people (25-45 years of age)(77).

[0077] In a series of three double blind, placebo controlled crossover trials performed by the team of Dr. Hindmarch at the University of Leeds on healthy volunteers (aged 25-40), results demonstrated a significant memory improvement. The method of objective evaluation included the Steinberg Memory Test. These significant improvements clearly demonstrate the efficacy of Vinpocetine on young and healthy individuals (78).

[0078] The present composition contains preferably from about 1mg to about 25mg, more preferably from about 2mg to about 20mg, and even more preferably from about 4mg to about 10mg of *Vinca minor*. Commercially available sources of the extract, such as BioVinca ™ distributed by Cyvex Nutrition, are suitable for use within the present composition.

K. *Huperzia serrata* (Huperzine A)

[0079] Huperzine A is an extract from club moss (*Huperzia serrata*) that has been used in Chinese medicine for centuries to treat inflammation and fever. In recent years, interest in this extract has shifted to its effects on the brain. Huperzine A boosts neurotransmission by naturally decreasing the hydrolysis of the neurotransmitter acetylcholine through inhibition of the enzyme acetylcholinesterase (79). In addition, huperzine protects neurons from damage and decreases neuronal cell death. It has been shown to enhance memory and improve cognitive function. Specifically, huperzine administration has been demonstrated to enhance focus, concentration and memory (80, 81). For patients with Alzheimer's disease and serious dementia, this herbal extract may have profound benefits (80, 84, 85).

[0080] In one study carried out in China, fifty patients with Alzheimer's disease were given 200 micrograms of huperzine A in four divided doses, and fifty-three other patients with similar degrees of dementia were administered a placebo. Fifty-eight percent of the people treated with the herb had improvements in memory, cognitive function and behavior, compared to thirty-six percent who improved on the placebo (83).

[0081] Interestingly, huperzine A appears to produce its cognitive improvements with fewer side effects, and its actions are of longer duration than current drugs which perform in much the same manner (82).

[0082] *Huperzia serrata* extracts, preferably derived from the Lycopodium serrata, are used within the present compositions preferably from about 25mcg to about 200mcg, more preferably from about 40mcg to about l00mcg, and even more preferably from about 50mcg to about 75mcg.

[0083] In addition to the primary components discussed above, the present herbal composition may also contain other nutrients or herbal extracts that assist, directly or indirectly, in maintaining or restoring mental health by improving the memory, focus, concentration or mood of a patient. Examples of other suitable constituents for the present compositions are vitamins such as Vitamin D3 (calciferol); amino acids such as L-Glutamine and N-acetyl-L-Tyrosine; and herbal extracts such as the anthocyanides derived from the fruit of *Vaccinium myrtillus* (Billberry). An example

of the preferred formulation of the present composition and possible variants on the composition are provided below as Formulations I and II.

Formulation I

[0084] Formula I is provided in the following table:

Table 1. Formula I. Each 4 tablet serving contains the listed ingredients.

Ingredient		Amount[1]
Vitamin A (natural beta carotene/mixed natural carotenoids)		4000 IU
Vitamin D-3 (cholecalciferol)		100 IU
Vitamin E (natural d-alpha succinate)		30 IU
Vitamin B-l (mononitrate)		3 mg
Vitamin B-2 (riboflavin)		2 mg
Vitamin B-3 (50% each inositol hexanicotinate & niacinamide)		25 mg
Vitamin B-5 (d-calcium pantothenate)		12 mg
Vitamin B-6 (33% pyridoxal-5-phosphate & 66% pyridoxine alpha keto glutarate)		15 mg
Vitamin B-12 (cyanocobalmin as ion exchange resin)		20 mcg
Folic Acid		400 mcg
Biotin		300 mcg
Vitamin C (16.67% each:	ascorbic acid sodium ascorbate ascorbyl palmitate calcium ascorbate potassium ascorbate zinc ascorbate)	250 mg
Calcium (33% each:	citrate ascorbate succinate	50 mg
Magnesium (33% each:	citrate malate taurinate	100 mg
Potassium (33% each:	citrate aspartate ascorbate	50 mg
Iron (Ferronyl® from Albion Labs)		5 mg
Zinc (citrate Ascorbate)		10 mg

[1] IU = international units; mg = milligram; mcg = microgram.

Ingredient	Amount[1]
Manganese (citrate)	2 mg
Iodine (kelp)	15 mcg
Copper (citrate Chelazome® from Albion Labs)	0.4 mg
Chromium (polynicotinate)	100 mcg
Selenium (selenomethionine)	20 mcg
Molybdenum (amino acid chelate)	10 mcg
DHA Concentrate (15% fish oil)	40 mg
Phosphatidyl Serine (soy lecithin)	44 mg
Bilberry (standardized extract 25%)	10 mg
Activin® (grape seed and grape skin extract)	10 mg
N-Acetyl-L-Tyrosine	10 mg
Inositol	25 mg
L-Pyroglutamic Acid	50 mg
L-Glutamine	105 mg
DMAE (bitartrate)	271 mg
PAK (pyridoxal-alpha ketoglutarate)	25 mg
Bacopa/Bacopin®	50 mg
GABA	10 mg
Choline (bitartrate)	25 mg
Vinpocitine	5 mg
Huperzine Extract	50 mcg
Boron (citrate)	20 mg
Vanadium (vanadyl sulfate)	5 mcg
Trace-Lyte® (electrolyte concentrate from _____)	2 mg

Formulation II.

[0085] Formula II is the same as Formula I except that instead of 20 mcg (*i.e.*, micrograms) of selenium per 4 tablets there is 50 mcg of selenium per 4 tablets.

[0086] The exact proportions of the above-disclosed components may vary depending upon the concentration of active ingredients within the herbal compositions and the desire to optimize the bioavalability of these constituents of the composition. Using the guidance provided above and a basic knowledge of drug preparation and pharmacology, one skilled in the art could easily adjust the proportions of the separate components of the composition so as to obtain a composition which has the therapeutic affects discussed above and shown in the examples herein. The discussion of the proportions of ingredients in the composition provided above is merely meant as an example and is not intended to limit the scope of the present invention from including

any novel combination of the disclosed herbal and non-herbal components which have the intended effect of relieving the symptoms of pain, fever and inflammation, as discussed herein.

III. Preparation of the Compositions

[0087] The compositions of this invention can be used in the form of a dietary supplement, for example, in solid, semi-solid or liquid form which contains the ingredients of the present invention in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications.

[0088] The ingredients may be compounded, for example, with the usual non-toxic pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. Formulations of the present invention encompass those which include various combinations of the exemplified ingredients, as well as carriers such as water, talc, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid or liquid form. In addition, auxiliary, stabilizing, thickening and coloring agents and perfumes may be added as desired.

[0089] For preparing solid compositions such as tablets or capsules, the principal ingredients are mixed with a carrier (*e.g.*, conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums) and other diluents (*e.g.*, water) to form a solid preformulation composition containing a substantially homogeneous mixture of a compositions of the present invention, or a non-toxic salt thereof. When referring to the preformulation compositions as substantially homogenous, it is meant that the active ingredients are dispersed evenly throughout the compositions so that the compositions may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. These solid preformulation compositions are then subdivided into unit dosage forms of the type described above containing predetermined amounts of the compositions of the present invention, preferably in tablets or pills. Generally, a person ingests 1 to 8 pills per day of the compositions provided by this invention. More preferably, a person ingests 4 or 8 pills per day of the compositions provided by this invention. Most

preferably a person ingests 4 pills either once or twice a day to derive the benefits of the compositions provided by this invention.

[0090] The tablets or pills of the novel compositions can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablets or pills can comprise both an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

[0091] The liquid forms, in which the novel compositions of the present invention may be incorporated for administration orally or by injection, include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil as well as elixirs and similar administration vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic natural gums, such as tragacanth, acacia, alginate, dextran, sodium carboxymethyl cellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

[0092] Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for reconstitution with water or other suitable vehicles before use. Such liquid preparations may be prepared by conventional means with additives such as suspending agents (*e.g.*, sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters or ethyl alcohol); preservatives (*e.g.*, methyl or propyl p-hydroxybenzoates or sorbic acid); and artificial or natural colors and/or sweeteners.

[0093] The ingredients may be formulated for parenteral administration by injection, which includes using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules, or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may

contain formulating agents such as suspending, stabilizing, and/or dispersing agents. Alternatively, the active ingredients may be in powder form for reconstitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[0094] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth and as follows in the scope of the appended claims.

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